REMARKS

The Office Action dated July 2, 2004 has been carefully reviewed and the foregoing amendment and the following remarks are made in response thereto. In view of the amendment and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendment. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. Claim 21 has been amended to incorporate the limitation of at least five genes in claim 36. Claim 21 is further amended to point out that the comparison is made among the first, second, and third expression profiles. Support for the amendment can be found in examples 12, 13, and 14 on pages 45-48 of the specification. Claims 35 and 36 have been canceled in view of the amendment of claim 21. As amended, claims 21, 34, 37-46 are current under consideration.

Summary of Office Action

1. Claims 21 and 34-46 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

2. Claims 21 and 34-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 21, 34, 35, 44-46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rohrer *et al.* (U.S. Patent No. 6,335,174).

4. Claims 42 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rohrer *et al.* (U.S. Patent No. 6,335,174) in view of Chee (cited in the IDS).

The Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 21 and 34-46 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way to enable one skilled in the art to make or use the claimed invention.

The Examiner alleges that the specification has not provided sufficient guidance to enable the skilled artisan to diagnose a disorder by comparing the expression pattern of T

lymphocytes from a subject to the expression profile of T lymphocytes from reference normal or inflammatory disease states or from other disease states (Office Action, page 3). More specifically, the Examiner asserts that the specification does not provide any specific gene profiles that conclusively represent a normal or inflammatory disease state. The Examiner then reasons that there is no predicative means in the specification for determining which nucleic acid combination is specifically up-regulated or down regulated and one of skill in the art is not provided with any reasonable expectation that she could obtain a gene expression profile specific for a particular disease without undue experimentation (Office Action, page 8).

Applicants respectfully disagree. The specification is believed to be fully enabling for Applicants' claims. The guidance and direction given in Applicants' disclosure, including the Examples and Tables contained therein, considered with the skill of the ordinary worker in the art, are more than adequate to enable the full use of the invention.

Applicants further respectfully submit that the Examiner has not provided a reasonable basis to support this assertion and, to the contrary, Applicants believe that a person skilled in the art would in fact have a very reasonable expectation of success by following Applicants' disclosure. The specification discloses a method of diagnosing a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD in a subject by examining gene expression profiles (see page 4, line 24, to page 5, line 3). The specification supports this general disclosure by specifically correlating gene expression in T lymphocytes with those diseases to be diagnosed because these expression profiles normally have unique patterns of cDNA species which correspond to T cell mRNA species encoded by genes that are modulated by the inflammatory process (see page 46, lines 1-3).

In addition, the specification discloses that genes, such as those listed in Figures 4 and 5, can serve as markers for various T cells that have been activated by antigens, pathogens, or other inflammatory mediators. Similar gene expression profiles can be obtained from a subject to be diagnosed. The expression profile of the diagnosed subject can then be compared to the expression profile prepared from a patient having one of the diseases to determine if the expression profiles are similar as compared to a normal control, thereby diagnosing whether the subject has a sterile inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.*. As such, the specification provides specific examples of

diagnosing a sterile inflammatory, autoimmune disorders, or immunodeficiency disorders (see Example 13, page 46) and GVHD (see Example 14, page 47) by comparing the gene expression levels in T lymphocytes. The specification discloses more than 30 genes in Figures 4 and 5 as examples and teaches that the up-regulation or down-regulation of these genes, such as the gene encoding human serine esterase, may be used as markers of the diseases. In view of this disclosure, Applicants respectfully submit that one skilled in the art can prepare gene expression profiles of T lymphocytes from a control subject, a disease subject and a subject to be diagnosed, compare the expression levels of the genes in the profiles, and determine whether the subject to be diagnosed has the disease.

Applicants respectfully submit that preparing a gene expression profile from T cells *per se* is routine for the person skilled in the art. Further, the present specification at pages 15-31 provides guidance for those skilled in the art how to prepare gene expression profiles by differential display, hybridization of samples to arrays, etc. Since the detection of gene expression is routine, one of ordinary skill in the art would have no difficulty preparing the gene expression profiles as claimed, diagnosing a disease state by comparing gene expression profiles from T cells from a subject to be diagnosed to the expression profiles from T cells from a subject that has a sterile inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.*. If the expression profiles are similar as compared to a normal control, one of skill in the art can readily diagnose the subject to have one of those diseases.

Because the generation of gene expression profiles is routine and the comparison of such expression profiles is well described in the specification, one skilled in the art can practice the present invention without undue experimentation. The invention is thus enabled. To question the operability of the applicants' invention, the Examiner has the initial burden to provide a reasonable explanation as to why the scope of protection provided by the claim is not adequately enabled by the disclosure. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Examiner has failed to do so as she has not identified any documentary evidence or technical reasoning substantiating those doubts. Without a reason to doubt the truth of the statements made in the present application, the application must be considered enabling.

The Examiner further alleges that that there is no teaching in the specification as to the identity or number of genes that are up-regulated or down-regulated in a sterile

inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.*. Applicants respectfully submit that the identity or number of genes up- or down regulated in T cells in various disease states does not need to be disclosed to diagnose a sterile inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.* as claimed. The instant claims merely involve diagnosing a disease by comparing the gene expression profiles. As claimed, the gene profiles may contain as few as five genes or as many as 1,000 or more genes. As long as the same genes are compared, one skilled in the art is able to determine whether the gene expression profile from a subject to be diagnosed is similar to that of a patient with the disease and subsequently make a correct diagnosis. For purposes of practicing the present invention, one skilled in the art need not have an understanding of all the genes up- or down-regulated by the disease process. As disclosed in the specification, the artisan merely needs to prepare profiles from various samples and compare those gene expression profiles to achieve the diagnostic purposes.

In response to the Examiner's arguments on pages 7 and 8 of the Office Action that the specification does not teach the "novel aspects of the invention," Applicants respectfully submit that pending claims are novel over prior art and that the recited method steps adequately define the novelty of the claimed invention. Applicants note that no art has been cited against the claims under 35 U.S.C. § 102. All that is required to make and compare the gene expression profiles as claimed are the T-cell samples and the teachings of the instant specification.

In sum, in view of the above amendments and remarks, it is submitted that Applicants have satisfied the enablement requirement mandated by 35 U.S.C. § 112, first paragraph. Accordingly, it is urged that the Examiner's § 112 first paragraph rejection should be withdrawn and the claims allowed.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 21 and 34-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Examiner asserts that the claims do not clearly set forth the relationship between the comparing and determining steps and do not clearly indicate how the comparison step results in the determination of the disease. Without

conceding the correctness of the Examiner's rejection, claim 21 has been amended to recite that the diagnosis is determined by comparing the first expression profile from the subject to be diagnosed to the second expression profile from a subject having a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD and the third expression profile from a normal subject. If the first gene expression profile is similar to the gene expression profile of a patient having a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD as compared to the normal profile, then a correct diagnosis of the disease can be made. In light of the amendment, Applicants respectfully request reconsideration and withdrawal of the rejection.

The Rejection under 35 U.S.C. § 103(a)

Claims 21, 34, 35, 44-46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rohrer *et al* (U.S. Patent No. 6,335,174). The Examiner contends that the claim are obvious in view of Rohrer's disclosure of comparing the T lymphocyté mRNA levels of IL-2, IFN-y, IL-4 and IL-10 of a test subject to the T lymphocyte mRNA levels of IL-2, IFN-y, IL-4 and IL-10 from a control subject and a subject having cancer to diagnose cancer.

As amended, claim 21 incorporates the limitation of original claim 36 which is not subject to the obviousness rejection in view of Rohrer. The difference between Rohrer and claim 36 is that claim 36 recites a gene expression profile of at least five genes whereas Rohrer discloses comparison of only four genes, IL-2, IFN-y, IL-4 and IL-10. In addition, Rohrer does not teach or suggest diagnoses of diseases other than cancer. Because Rohrer only teaches comparison of the expression level of four specific genes related to cancer, it would not have been obvious to one skilled in the art to prepare a gene expression profile of at least five genes for diagnoses of various T cell mediated diseases. Thus, Applicants assert that neither claim 21 nor its dependent claims are obvious. Accordingly, Applicants respectfully request the rejection be withdrawn.

Claims 42 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rohrer *et al* (U.S. Patent No. 6,335,174) in view of Chee *et al.* Applicants respectfully traverse. With respect to the primary Rohrer reference, the Examiner is directed to the discussions of the § 103 rejection above. As indicated, Rohrer does not disclose or suggest preparing and comparing a gene expression profile of at least five genes. The second cited

reference, Chee *et al.*, does not provide what Rohrer lacks. Chee does not teach preparing and comparing a gene expression profile of at least five genes. Chee only teaches methods for assaying for gene expression on a solid support. Accordingly, even if these references were combined, the combination of Rohrer and Chee does not provide Applicant's claimed method of diagnosing a disease based on a gene expression profile of at least five genes. Applicants respectfully request the rejection be withdrawn.

Conclusion

Applicants respectfully request reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is requested to contact the Applicants' undersigned representative.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: **January 3, 2005**

Respectfully submitted,
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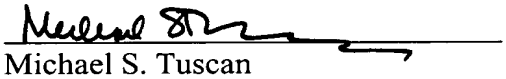

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